

< 50 % yield at -20°C , whereas $\text{Yb}[\text{OTf}]_3$ provided **23** in 72 % yield at room temperature.

- [11] For a review on $\text{Yb}[\text{OTf}]_3$ in synthesis see: S. Kobayashi, *Synlett* **1993**, 689.
- [12] For a thorough review on spiroacetal formation see: W. Rasshofer, *Methoden Org. Chem. (Houben-Weyl)*, 4th ed. 1952-, Vol. E14a/2, **1991**, pp. 1–200.
- [13] Compound **27** was previously described by Nicolaou et al.^[2b] The spectral data obtained for **27** here ($[\alpha]_D^{25} = +5.0$ ($c = 0.26$, CHCl_3), IR, ^1H and ^{13}C NMR, HRMS) are fully consistent with those reported in reference [2b].
- [14] For the assignment of methylene protons, the higher field proton was suffixed by a (e.g., H_a), while the lower field proton was suffixed by b (e.g., H_b).

Total Synthesis of Fostriecin (CI-920)**

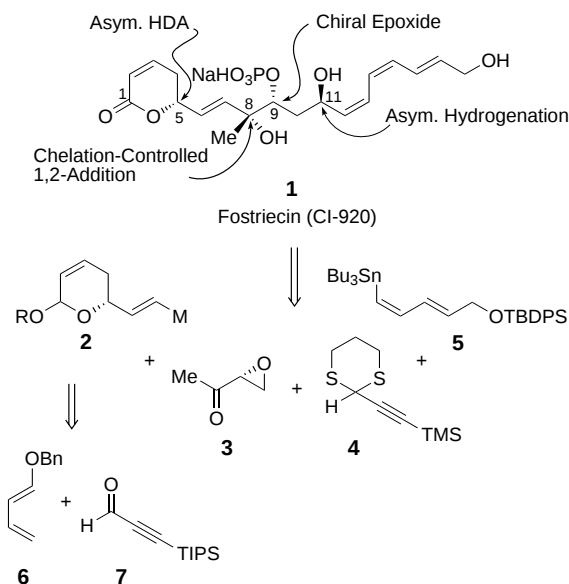
David E. Chavez and Eric N. Jacobsen*

Fostriecin (CI-920, **1**; see Scheme 1) is a structurally interesting antitumor agent that was first isolated in 1983 by scientists at Warner Lambert-Parke Davis.^[1] It displays in vitro activity against a broad range of cancerous cell lines as well as in vivo antitumor activity,^[2] and it appears to operate by a novel mechanism involving inhibition of the mitotic entry checkpoint.^[3] In this context, fostriecin is a potent inhibitor of protein serine/threonine phosphatases, and it is in fact the most selective protein phosphatase inhibitor identified to date (10^4 times greater affinity for the protein phosphatases PP2A and PP4 versus PP1).^[4]

It was not until 1997 that a correct and complete stereochemical assignment of fostriecin was made by Boger and co-workers,^[5] and that was followed very recently by a report of the first total synthesis from the same group.^[6] Certainly, the development of a practical synthetic route to fostriecin is warranted based on its interesting biological properties. In addition, clinical trials carried out at the National Cancer Institute were halted early in Phase I over concerns about the stability and purity of the natural material.^[7] A flexible synthetic route to **1** could serve as a basis for the discovery of analogues with similar biological but more desirable physical properties. In addition, the structure of fostriecin poses an

assortment of interesting challenges to an efficient synthetic design, including the presence of the unsaturated lactone,^[8] the C8–C11 triol monophosphate component, and the conjugated *Z,Z,E*-triene unit. Herein we report a new total synthesis of fostriecin. Our approach integrates highly effective asymmetric catalytic reactions to generate key chiral building blocks, and efficient coupling reactions to enable their convergent assembly.

The synthetic plan involves assembly of four fragments (**2**–**5**) of similar complexity (Scheme 1). Epoxyketone **3** plays a central role in our strategy, serving not only as the source of



Scheme 1. Retrosynthetic analysis of **1**. TBDPS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl

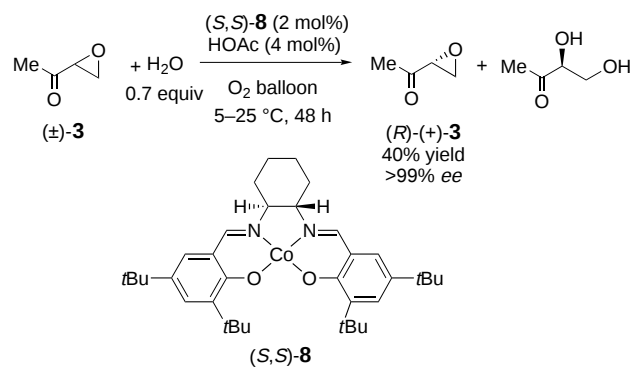
the C9 stereocenter, but also as a lynchpin for joining the left-hand vinyl lactone unit **2** and the right-hand triene diol fragment. We anticipated applying the [(salen)Co]-catalyzed hydrolytic kinetic resolution (HKR) reaction to the preparation of enantioenriched **3**, encouraged by the remarkable generality displayed by this method for the preparation of highly enantioenriched terminal epoxides.^[9] However, while racemic **3** was prepared easily from inexpensive methyl vinyl ketone,^[10] its HKR proved particularly challenging. Under standard conditions ((*S,S*)-**8**, 0.2–2 mol %, 0.55 equiv H_2O), precipitation of catalyst as the reduced [(salen)Co^{II}] complex was observed with low substrate conversion.^[11] Fortunately, this problem proved relatively easy to circumvent. When the reaction was carried out under an atmosphere of O_2 instead of N_2 or air, reduction of catalyst was avoided and the HKR proceeded to completion affording **3** in > 99 % *ee* and 40 % yield (Scheme 2; possible yield = 50 %).

With an effective route to (*R*)-**3** in hand, the next key consideration in the synthesis was the diastereoselective addition of a vinyl organometallic such as **2** to the carbonyl group of **3** to assemble the two left-hand fragments and set the C8 tertiary alcohol stereocenter. While addition of Grignard reagents to **3** proceeded in THF with exclusive reaction at the ketone functionality, only modest diastereoselectivity (ca. 4:1)

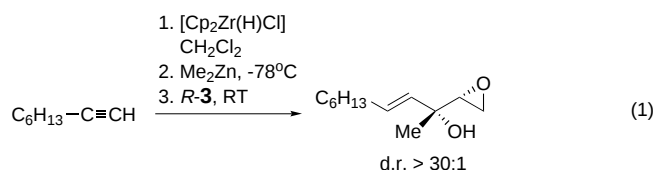
[*] Prof. E. N. Jacobsen, D. E. Chavez
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-496-1880
E-mail: jacobsen@chemistry.harvard.edu

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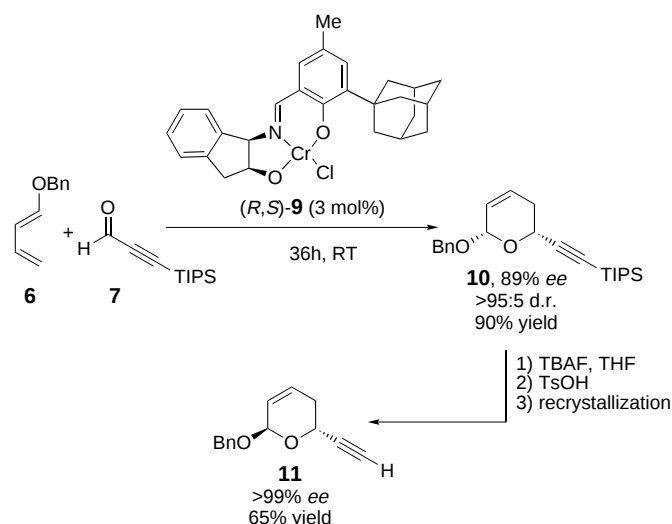
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Scheme 2. Hydrolytic kinetic resolution of epoxyketone **3**.

was observed with the desired chelation control product predominating. A variety of alternative methods for addition of vinylorganometallic reagents to **3** was investigated, and the protocol developed by Wipf and co-workers^[12] for the addition of vinyl zinc intermediates to aldehydes proved most effective. For example, hydrozirconation of model substrate 1-octyne, transmetalation with dimethylzinc and addition to **3** led to the isolation of the desired 1,2-addition adduct in good yield (75 %) and with excellent diastereoselectivity (>30:1); the chelation control product was favored [Eq. (1)]. This represents the first extension of the Wipf methodology to ketone vinylation.



Having established a plausible strategy for coupling of fragments **2** and **3**, we sought an efficient enantioselective method for the preparation of alkynyl lactone **10** (Scheme 3).

Scheme 3. Preparation of **11** by means of the asymmetric hetero-Diels–Alder reaction catalyzed by **9**.

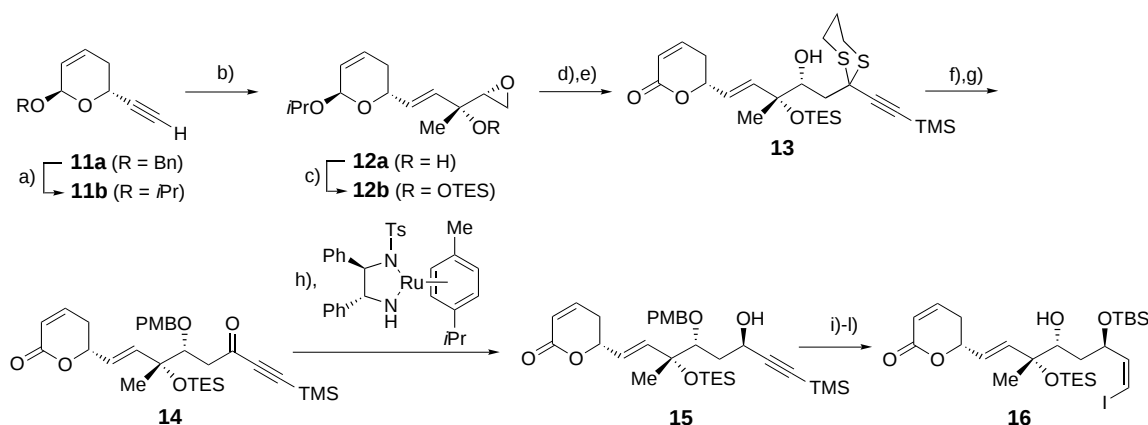
We were particularly intrigued by the possibility of applying the recently developed Cr-catalyzed hetero-Diels–Alder (HDA) reaction to this task, having established in earlier studies that cycloadditions between 1-methoxybutadiene and simple aldehydes are catalyzed by complex **9** with high enantioselectivity.^[13] In the ideal case, it would be possible to establish the entire carbon framework of the left-hand fragment **2** in the HDA reaction, and with that in mind we investigated the reaction of alkoxybutadiene derivatives with ynal **7**. We were pleased to find that **7** was indeed an effective partner in the asymmetric HDA reaction, affording cycloadducts in good yield, diastereoselectivity and enantioselectivity (Scheme 3). Whereas a variety of 1-alkoxybutadiene derivatives underwent reaction with >95 % *de* and >85 % *ee*, benzyloxy derivative **6** led to product with highest yield. Desilylation of **10** with tetrabutylammonium fluoride (TBAF), followed by acidic workup, was accompanied by epimerization of the acetal to the more stable α -anomer **11a**. This intermediate underwent recrystallization to enantiomeric purity in good overall yield.

With the two left-hand chiral building blocks now readily accessible in >99 % *ee*, we investigated their coupling using the Wipf procedure described above. Under carefully optimized conditions,^[14] hydrozirconation/transmetalation of **11b** was followed by reaction with **3** to afford the desired addition product **12a** with excellent diastereoselectivity (>30:1; Scheme 4). Although the yield for this novel vinylation reaction was modest, this coupling enabled introduction of the C8 stereocenter with high selectivity at an early stage in the synthesis and provided advanced intermediate **12a** in only seven steps (five in the longest linear sequence) from commercially available materials.

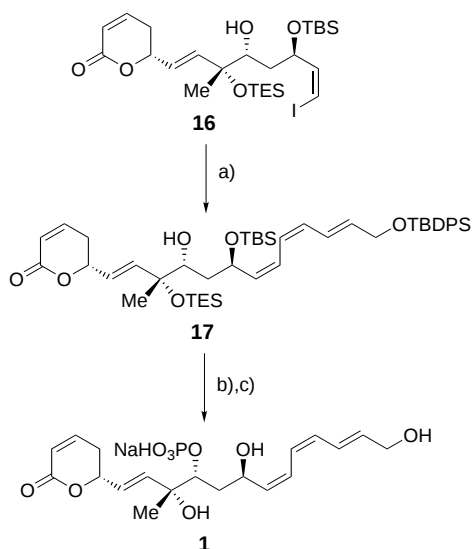
The tertiary alcohol was protected to give silyl ether **12b**, and epoxide ring opening with the anion derived from dithiane **4**^[15] proceeded in excellent yield to accomplish the second fragment coupling. Acetal hydrolysis followed by selective oxidation of the resulting lactol in the presence of the free secondary C9 alcohol provided **13**. Dithiane removal using Stork's protocol,^[16] followed by protection of the secondary alcohol as PMB ether^[17] **14** afforded the C8–C9 diol unit in orthogonally protected form, in anticipation of a later stage selective phosphorylation of the C9 alcohol.

The final stereocenter (C11) was established by using Noyori's transfer hydrogenation methodology.^[18] The catalytic asymmetric reduction allowed us to control the relative stereochemistry of the 1,3-diol unit simply by selection of the appropriate enantiomer of the catalyst.^[19] The reaction proceeded with high selectivity to provide **15** (d.r. >25:1).^[20] Protection of the propargylic alcohol as a silyl ether, one-pot acetylene deprotection and iodination,^[21] followed by PMB deprotection and *cis*-vinyl-iodide formation using a highly selective diimide reduction^[22] provided vinyl iodide **16** (Scheme 4).

The final fragment coupling joined vinyl iodide **16** and the *Z,E*-stannane **5** (Scheme 5).^[23] The cross-coupling was effected under ligand-free Stille coupling conditions^[24] and proceeded with complete retention of olefin stereochemistry. Phosphorylation of the C9 alcohol of **17** was accomplished by using a modification of the protocol developed by Evans.^[25]



Scheme 4. Synthesis of the C₁–C₁₃ fragment. a) TsOH, *i*PrOH, 90%; b) [Cp₂Zr(H)Cl], CH₂Cl₂; then Me₂Zn, –78 °C, 10 min; then **3**, 4 h, RT; c) TESCl, imidazole, DMF; 45%, 2 steps; d) *n*BuLi, **4**, THF, –40 °C; then **12b**; 89%; e) PPTS, acetone/H₂O (4:1); then MnO₂, CH₂Cl₂; 65%, 2 steps; f) bis(trifluoroacetoxyiodobenzene), MeOH/H₂O (9:1); 70%; g) 4-MeO-benzyl trichloroimidate, Ph₃C⁺ BF₄[–], Et₂O; 83%; h) *i*PrOH; 36 h; 93%, >95:5 dr; i) TBSOTf, 2,6-lutidine, CH₂Cl₂; 80%; j) AgNO₃, NIS, acetone; 95%; k) DDQ, CH₂Cl₂; 100%; l) NBSH, THF/*i*PrOH (1:1), TEA; 85%; TES = triethylsilyl; TESCl = chlorotriethylsilane; TsOH = *p*-toluenesulfonic acid; PPTS = pyridinium *p*-toluenesulfonate; PMB = *p*-methoxybenzyl; TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate; NIS = *N*-iodosuccinimide; DDQ = dichlorodicyanoquinone; NBSH = *o*-nitrobenzenesulfonylhydrazide; TEA = triethylamine; PMBOH = *p*-methoxybenzyl alcohol.



Scheme 5. Completion of the synthesis of fostriecin. a) [PdCl₂(CH₃CN)₂], **5**, DMF; 85%; b) PCl₃, pyr; then PMBOH; then *t*BuOOH, CH₂Cl₂; 65%; c) HF, CH₃CN; then pyr; 45%.

Global deprotection of the silyl and *p*-methoxybenzyl groups afforded **1**, with spectroscopic and chromatographic properties identical to those of natural fostriecin.

The synthesis of fostriecin was thus completed in 17 steps in the longest linear sequence. Our approach made use of asymmetric catalytic reactions to obtain building blocks **11** and **3** in >99% *ee*. Epoxycetone **3** is now readily accessible using HKR methodology, and holds promise as a versatile chiral building block for asymmetric synthesis. In the context of the fostriecin synthesis, the use of **3** allowed rapid access to advanced intermediate **13** through selective ketone alkylation and subsequent epoxide ring opening. Overall, control of three of the four stereocenters of fostriecin was exerted by means of asymmetric catalytic reactions, while the tertiary C8 allylic alcohol center was installed by using a novel, highly

diastereoselective alkenylation of epoxycetone **3**. This synthesis further illustrates the power of the chiral building block strategy for natural product synthesis, and provides easy access to structural analogues of fostriecin for further study.

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